REMARKS/ARGUMENTS

Claims 31-33 remain pending in this application. Claims 1, 10, 21-24, 27-30 and 34-36 have been canceled by this paper. Claim 31, previously dependent from Claim 1, has been amended to be independent.

Election /Restrictions

Applicants acknowledge that the specie election has been modified to include all compounds of the formula of claim 29 as a single specie. Applicants note that the specie of canceled Claim 29 is the same as for pending Claim 32.

The Examiner notes that the expression "'ACAT inhibitors' in claims 28-36 renders claims 28-36 unclear." The specification at page 6, lines17-18 points out that acyl-coenzyme A:cholesterol acyltransferase is referred to by the acronym ACAT (by including ACAT in parentheses after the full name). The term ACAT is well known in the art. As such it is readily understood by those of skill in the art that an "ACAT inhibitor" is an inhibitor of acyl-coenzyme A:cholesterol acyltransferase. As noted in the specification at page 6, lines 18-19, ACAT inhibitors are well-known in the art. For these reasons, Applicants assert that the claims containing the term ACAT inhibitor are not unclear.

Rejection under 35 USC§112, first paragraph

The Examiner has rejected Claims 10, 21-24 and 27-36 under 35 USC§112, first paragraph because "the instant claims are drawn to the methods for **preventing** the onset of Alzheimer's disease." (emphasis in original). To expedite prosecution of the claims, each of the rejected claims has been canceled without prejudice to the filing of a divisional application to the canceled subject matter. Claims 10, 21-24, 27-30 and 34-36 have been canceled. Claims 31-33 are not directed to a method of preventing and applicants believe these claims were inadvertently included in this rejection. Applicants believe that the cancellation of claims 10, 21-24 and 27-30 renders the Examiner's rejection moot and therefore request withdrawal of this rejection.

Rejection under 35 USC§112, second paragraph

The Examiner states that "[c]laims 28-36 contain the trademark/trade name ACAT." Applicants assert that ACAT is not a trademark/tradename, but rather an acronym for acyl-coenzyme A:cholesterol acyltransferase. As noted above, this acronym is commonly used by those of skill in the art. The acronym is given in the specification at page 6, lines17-18. Applicants respectfully traverse this rejection and request reconsideration and withdrawal of this rejection.

Rejection under 35 USC§102(b)

The Examiner has rejected Claims 1, 21-24 and 27 under 35 USC§102(b) as being anticipated by Scolnick (WO95/06470). The Examiner has also rejected claims 1, 10, 21-24 and 27 as being anticipated by JP8143454.

Claims 1, 10, 21-24 and 27 have been canceled thus rendering these rejections moot. Therefore Applicants request withdrawal of these rejections.

Rejection under 35 USC§103

The Examiner has rejected Claims 27-36 under 35 USC§103 over Lee et al. (US Pat No. 5,491,172) in view of Scolnick (WO95/06470). Claims 31-33 are currently pending.

Lee discloses a genus of ACAT inhibitors and their utility for treating hypercholesterolemia and atherosclerosis. As noted by the Examiner, Lee does not "disclose that the instant claimed compound may be useful in methods of treating the onset of Alzheimer's disease." There is no mention of Alzheimer's disease in the Lee reference.

Scolnick discloses that HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin and fluvastatin) may be useful to lower Apolipoprotein E isoform 4 (Apo E4) to treat and prevent Alzheimer's disease. Scolnick does not disclose nor discuss the use of ACAT inhibitors in the treatment of Alzheimer's disease (AD).

For the reasons given below, Applicants respectfully assert that it would not have been obvious to one skilled in the art, in view of Lee and Scolnick, that ACAT inhibitors would be useful in the treatment of Alzheimer's disease. There was no motivation in either Lee or Scolnick to substitute ACAT inhibitors in the methods of Scolnick to arrive at the presently claimed invention. Even if there was motivation to combine the references there would not have been a reasonable expectation of success.

MPEP section 706.02(j) states that in order to establish a prima facie case of obviousness, three basic criteria must be met.

1. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.
2. There must be a reasonable expectation of success.
3. The prior art references must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and **not** based on applicant's disclosure. MPEP section 706.02(j) (emphasis added).

One of skill in the art at the time the present application was filed, would not have been motivated by either Lee or Scolnick to combine the two references. Lee describes a genus of compounds that block the absorption of cholesterol from the intestine and does not involve compounds or methods which inhibit the de novo biosynthetic pathway. Lee has no mention of Alzheimer's disease. There is nothing in Lee that would lead one of skill in the art to use an ACAT inhibitor in place of the disclosed ACAT inhibitors. Nor is there anything in Scolnick which would have provided motivation to combine the two references. In fact, when viewed in the context of art available before the filing of this application, the disclosure of Scolnick teaches away from the utility of an ACAT inhibitor in the treatment of AD.

Scolnick discloses a method of treating, arresting the development of and preventing Alzheimer's disease by regulating the amount of Apo E isoform 4 circulating in the bloodstream

and in the brain by treating with a statin. The Examiner posits that Scolnick "teaches that reduction of cholesterol and plasma-triglyceride and LDLC levels may decrease risk of development of Alzheimer's disease and treat vascular related diseases such as Alzheimer's disease." Applicants assert that the Examiner has not properly characterized Scolnick. Applicants cannot locate anywhere in Scolnick where it is taught that reduction of "plasma-triglyceride and LDLC levels may decrease risk of development of Alzheimer's disease." Rather, Scolnick discusses on page 10 that it is desirable to decrease circulating blood levels of ApoE isoform 4. The data in Scolnick show that ApoE levels go down in patients treated with lovastatin. (Example 1) and most dramatically in patients who are homozygous for ApoE isoform 4. Scolnick also gives a hypothetical example, Example 2, describing how one would assess the levels of ApoE in Alzheimer's patients homozygous for ApoE type 4 allele after treatment with a statin. Scolnick does not provide any data for total cholesterol levels after statin treatment. The focus of Scolnick is on **lowering ApoE levels with a statin for the treatment of Alzheimer's disease.**

One of skill in the art could not conclude, from the disclosures of Lee and Scolnick, that ACAT inhibitors would have utility in treating AD. Furthermore, one of skill in the art would not have been motivated to substitute an ACAT inhibitor for the methods of Scolnick.

Even taking Scolnick at face value and assuming that one would have wanted to lower ApoE levels, one of skill in the art would not have chosen ACAT inhibitors for this purpose. The ACAT inhibitor CI-1011 has been shown to elevate HDL-C, and would therefore be expected to raise the levels of Apo E in the serum. (J. Med. Chem., 1996, 39, 5031-5034). Thus, based on the art available at the time the present application was filed, one of skill in the art would not have been motivated to substitute ACAT inhibitors for statins in the methods of Scolnick.

Further one of skill in the art would not have been motivated to substitute ACAT inhibitors for statins in the methods of Scolnick because the mechanisms by which statins and ACAT inhibitors operate are very different. Even if it is assumed there was motivation, there would not have been a reasonable expectation of success because of the differences in these mechanisms.

Cholesterol in the body comes from two sources, dietary cholesterol from food and cholesterol that is synthesized by the body. The enzyme acyl-CoA:cholesterol acyltransferase

(ACAT) is involved in the uptake of dietary cholesterol or the reabsorption of cholesterol which has been previously released into the intestine through the body's own regulatory action. ACAT inhibitors inhibit ACAT, the action of which is required for the uptake of dietary cholesterol into the blood stream. Dietary cholesterol is taken up by the intestinal mucosal cells wherein ACAT catalyzes the esterification of cholesterol. The cholesterol esters are packaged into the chylomicrons which are then released into the blood stream. See Lee et al. (US Pat No. 5,491,172) column 1, lines 50-60.

In contrast, statins affect the de novo biosynthesis of cholesterol in the body. Lovastatin, and statins in general, inhibit the enzyme HMG CoA reductase which is one of the enzymes in the cholesterol biosynthesis pathway. HMG CoA reductase catalyzes the conversion of HMG-CoA to mevalonate. mevalonate is one of at least seven intermediates between HMG-CoA and cholesterol. Statins thus would affect the levels of these intermediates, some of which have been shown to participate in pathways other than the cholesterol synthesis pathway.

The data in Scolnick do not distinguish between whether the effect of lovastatin is due to its cholesterol lowering effects or is due to another mechanism, in fact Scolnick focuses on the effect of lovastatin on Apo E isoform 4 levels. For example, it may be that decreased levels of mevalonate, rather than lower total cholesterol levels, resulted in the lower levels of ApoE. There is nothing in Lee or Scolnick that would motivate one of skill in the art to substitute an ACAT inhibitor for a statin in the methods disclosed in Scolnick. Furthermore, there is nothing in Lee or Scolnick that would have provided a reasonable expectation of success that ACAT inhibitors would be useful for the treatment of Alzheimer's disease. It is the present application that is the first disclosure that ACAT inhibitors do indeed have that utility.

β-amyloid (Aβ) is the principal proteinaceous component of amyloid associated with Alzheimer disease (AD). Aβ is viewed as a likely underlying cause of the degeneration and dementia that characterizes AD. Applicants' disclosure shows that total cholesterol and LDL cholesterol are correlated with levels of β-amyloid (page 14, lines 3-24, and figure 1). In addition, Applicants' disclosure shows that both statins and ACAT inhibitors lower Aβ in Chinese Hamster Ovary (CHO) cells that have been engineered to over-express human β-amyloid precursor protein. (p16, Example 2). Applicants' also show that, consistent with these CHO data, levels of Aβ in the brains of animals are reduced in response to treatment with

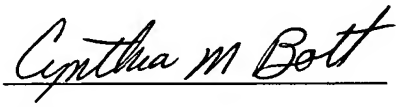
simvastatin. It is Applicants' data that gives credible support for the conclusion that ACAT inhibitors are useful for the treatment of AD.

In conclusion, the Examiner cannot rely on the Applicants' disclosure to make up for the deficiencies of the cited references. Because there was no motivation in either Lee or Scolnick to substitute ACAT inhibitors in the methods of Scolnick to arrive at the presently claimed invention, nor was there a reasonable expectation of success, Applicants assert that Claims 31-36 are patentable and request withdrawal of the rejection under 35 USC§103

Applicants respectfully request reconsideration and withdrawal of all of the rejections in light of the amendments and remarks made herein and allowance of all the pending claims.

Respectfully submitted,

Date: August 7, 2003



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